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Toxicology in the critically ill patient

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General approach to the intoxicated patient

The protean nature of intoxications leads to potential misdiagnosis. Therefore, a high index of suspicion for intoxication is warranted in critical care medicine. Identification of a toxidrome further helps in this regard (Table 1).

Epidemiology

In their 2000 annual report, the American Association of Poison Control Centers reported a total of 2,168,248 human toxic exposure cases. Only 3% required critical care. Nine hundred and twenty fatalities were reported that occurred most commonly with analgesics, antidepressants, sedatives/hypnotics/antipsychotics, stimulants, ''street'' drugs, cardiovascular drugs, and alcohols. Mortality was greater in intentional, rather than unintentional, exposures. [1]

Diagnosis of toxic ingestion

History and physical examination

Because the history may be unreliable or incomplete [2], clinicians should pay attention to clinical features that are suggestive of a toxic ingestion (Box 1). Separating patients who have suspected poisoning into broad categories that are based on vital signs, eye findings, mental status, and muscle tone helps to determine drug or toxin class (Tables 2, 3) [3].

Laboratory evaluation

Three gaps are important in toxicology: the anion gap, the osmolal gap, and the oxygen saturation gap. Toxicology screening may confirm toxin exposure, but rarely alters management.

Anion gap

Depending on the institution, a normal anion gap may vary between 3 mEq/L and 12 mEq/L. An increase in the anion gap to greater than 20 mEq/L strongly suggests an organic acidosis (Boxes 2, 3). The anion gap may not be elevated in the setting of an organic acidosis if a concurrent condition that lowers the anion gap exists (eg, hypoalbuminemia). Many toxins do not increase the anion gap, whereas others (eg, lithium) decrease the anion gap [4].

Osmolal gap

Low molecular weight drugs and toxins increase the discrepancy between measured and calculated plasma osmolality (Box 4). Normal plasma osmolality is 285 to 295 mOsm. Freezing point depression osmometry, which is the most frequently used method, is capable of measuring ethylene glycol, ethanol, and methanol. Vapor pressure osmometry does not detect volatile alcohols, such as ethanol and methanol; however, it does detect ethylene glycol [5,6]. Normal osmolal gap ranges from −9 mOsm to +5 mOsm; 10 mOsm is considered the upper limit of normal, but an osmolal gap of 8 mOsm in a patient who started at − 9 mOsm may be elevated [7,8].

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Table 1
Common toxidromes

Toxidrome	Features	Drugs/toxins	Drug Treatment
Anticholinergic "Hot as a hare, dry as a bone, red as a beet, mad as a hatter"	Mydriasis Blurred vision Fever Dry skin Flushing Ileus Urinary retention Tachycardia Hypertension Psychosis Coma Seizures Myoclonus	Antihistamines Atropine Baclofen Benztropine Tricyclic antidepressants Phenothiazines Propantheline Scopalamine Methylpyroline	Physostigmine (for life threatening events, do not use in cyclic antidepressant overdose because of potential worsening of conduction disturbances)
Cholinergic "*SLUDGE*"	*S*alivation *L*acrimation *U*rination *D*iarrhea *G*I cramps *E*mesis Wheezing Diaphoresis Bronchorrhea Bradycardia Miosis	Carbamate Organophosphates Physostigmine Pilocarpine	Atropine Pralidoxime for organophosphates
β-adrenergic	Tachycardia Hypotension Tremor	Albuterol Caffeine Terbutaline Theophylline	Beta-blockade (caution in asthmatics) Potassium replacement
β-and α-adrenergic	Hypertension Tachycardia Mydriasis Diaphoresis Dry mucus membranes	Amphetamines Cocaine Ephedrine Phencyclidine Pseudoephedrine	Benzodiazepines
Sedative-hypnotic	Stupor and coma Confusion Slurred speech Apnea	Anticonvulsants Antipsychotics Barbiturates Benzodiazepines Ethanol Meprobamate Opiates	Naloxone Flumazenil Urinary alkalinization for phenobarbital
Hallucinogenic	Hallucinations Psychosis Panic Fever Mydriasis Hyperthermia Synesthesia	Amphetamines Cannabinoids Cocaine Lysergic acid diethylamide (LSD) Phencyclidine (may present with miosis)	Benzodiazepines
Narcotic	Altered mental status Slow shallow breaths Miosis Bradycardia Hypotension Hypothermia Decreased bowel sounds	Dextromethorphan Opiates Pentazocine Propoxyphene	Naloxone

(*continued on next page*)

Table 1 (*continued*)

Toxidrome	Features	Drugs/toxins	Drug Treatment
Serotonin	Irritability Hyperreflexia Flushing Diarrhea Diaphoresis Fever Trismus Tremor Myoclonus	Fluoxetine Meperidine Paroxetine Sertraline Trazodone Clomipramine	Benzodiazepine Withdrawal of drug Cyproheptadine
Solvent	Lethargy Confusion Headache Restlessness Incoordination Derealization Depersonalization	Hydrocarbons Acetone Toluene Naphthalene Trichloroethane Chlorinated hydrocarbons	Avoid catecholamines Withdrawal of toxin
Uncoupling of oxidative phosphorylation	Hyperthermia Tachycardia Metabolic acidosis	Aluminum phosphide Salicylates 2,4-dichlorophenol Dinitrophenol Glyphosate Phosphorus Pentachlorophenol Zinc phosphide	Sodium bicarbonate for metabolic acidosis Patient cooling Avoid atropine and salicylates Hemodialysis in refractory acidosis

Oxygen saturation gap

An oxygen saturation gap is present when there is more than a 5% difference between the saturation that is calculated from an arterial blood gas analyzer, which uses an assumed standard oxygen-hemoglobin dissociation curve, and the saturation that is measured by co-oximetry. Toxins that are associated with an increased oxygen saturation gap include: carbon monoxide, methemoglobin, cyanide, and hydrogen sulfide. Pulse oximetry may be unreliable in the setting of methemoglobinemia and may register falsely high in severe methemoglobinemia and falsely low in mild methemoglobinemia [9–11]. Carbon monoxide has a wavelength absorption coefficient that is similar to oxyhemoglobin; therefore it is registered as oxyhemoglobin by pulse oximetry which leads to overestimation of oxygen saturation when compared with co-oximetry [12,13]. An abnormally high venous oxygen content (arteriolization of venous blood) is characteristic of cyanide and hydrogen sulfide poisoning.

Toxicology screening

Screening tests rarely alter management [14,15]. Toxicology screening can identify a specific toxin for which an antidote is available, and, in some instances, quantify a toxin to allow for titrated therapy. Most institutions offer urine testing for six or seven of the most commonly abused drugs: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opioids, and phencyclidine. Results are generally available in 30 minutes. More comprehensive urine or serum screening are usually performed off-site and results are rarely available quickly [16]. Quantification of serum levels of alcohol (ethanol and nonethanol), acetaminophen, salicylate, phenobarbital, theophylline, digoxin, iron, and lithium are clinically important.

Initial supportive measures

Supportive measures, including the ABCs (airway, breathing, and circulation), may be required before confirmation of intoxication. With cervical spine precautions in place (unless trauma has been excluded) airway patency must be ensured in all cases. A ''cocktail'' of thiamine, dextrose, and naloxone should be administered to patients who have depressed mental status [17,18]. Regional Poison Control Center consultation is highly recommended in cases of suspected or confirmed poisoning.

Prevention of absorption

The route of entry for toxic substances can be dermal, ocular, gastrointestinal (GI), inhalational, or parenteral. Most cases that are managed by intensivists

Box 1. Clinical features that mandate consideration of toxic ingestion

- Past history of drug overdose or substance abuse
- Suicidal ideation or previous suicide attempt
- History of other psychiatric illness
- Agitation and hallucinations
- Stupor or coma
- Rotary nystagmus
- Delirium or confusion
- Seizures
- Muscle rigidity
- Dystonia
- Cardiopulmonary arrest
- Unexplained cardiac arrhythmia
- Hyper/hypotension
- Ventilatory failure
- Aspiration
- Bronchospasm
- Liver failure
- Renal failure
- Hyper/hypothermia
- Rhabdomyolysis
- Osmolal gap
- Anion gap acidosis
- Hyper/hypoglycemia
- Hyper/hyponatremia
- Hyper/hypokalemia
- Polypharmacy

occur through the gastrointestinal tract. There are four methods of gastrointestinal decontamination including three mechanical approaches (emesis, gastric emptying or lavage, and whole bowel irrigation) and the use of activated charcoal combined with a cathartic.

Emesis

Because of questionable efficacy (particularly when used hours after ingestion), in-hospital use of ipecac is decreasing [19]. There is little evidence that ipecac prevents any drug absorption or systemic toxicity [20] and there are no convincing data that it significantly alters the clinical outcome of patients who are alert on presentation to the emergency department.

Gastric emptying

Based on the available data, the American Academy of Clinical Toxicology does not recommend gastric lavage unless a patient has ingested a potentially life-threatening amount of a poison and the procedure can be undertaken within 60 minutes of ingestion [21]. The time limit may be extended to 12 hours in cases of poisoning with agents that delay gastric emptying, such as tricyclic antidepressants, opioids, or salicylates. In cases of ingestion of a caustic liquid, like kerosene or its derivatives, gastric lavage should be avoided because of the risk of aspiration-induced lung injury. Ensuring airway protection is imperative before gastric lavage.

Activated charcoal

Charcoal can be administered after gastric lavage, but more often it is used as the sole gastrointestinal decontaminating strategy. Activated charcoal is an effective adsorbant, except in cases of intoxication with alcohols, dichloro diphenyl trichloroethane (DDT), hydrocarbons, organophosphates, carbamates, acids, iron, and lithium. As with gastric lavage, ensuring adequate airway protection is important before use. Charcoal aspiration has been associated with pneumonia, bronchiolitis obliterans, acute respiratory distress syndrome, and death. Therefore, airway protection is imperative in stuporous, comatose, or convulsing patients.

Catharsis

Based on available data, the routine use of a cathartic in combination with activated charcoal is not endorsed by the American Academy of Clinical Toxicology or the European Association of Poison Centres and Clinical Toxicologists. If a cathartic is used, it should be limited to a single dose to minimize adverse effects [22].

Whole bowel irrigation

Whole bowel irrigation is indicated when activated charcoal is not anticipated to be effective (eg, iron or lithium overdose) or in cases of ‘‘body packing’’ with illicit drugs [23].

Enhancement of elimination

Forced diuresis and urinary pH manipulation

Routine use of volume loading to promote diuresis has not been well studied or supported in the literature and is not recommended. Urinary alkalinization (pH>7) with intravenous bicarbonate helps eliminate salicylates and phenobarbital; acetazolamide should not be used for this purpose because metabolic acidosis can increase the toxicity of certain poisonings (eg, salicylates). Urinary acidification (pH < 5.5) increases

Table 2
Drugs that affect temperature, heart rate, and pupil size

Hypothermia	Hyperthermia	Tachycardia	Bradycardia	Miosis	Mydriasis
Alcohols	Amphetamines	Amphetamines	Antiarrhythmics	Barbiturates	Amphetamines
Barbiturates	Anticholinergics	Anticholinergics	β-blockers	Carbamates	Anticholinergics
Cyclic antidepressants	Antihistamines	Antihistamines	Calcium channel blockers	Clonidine	Antihistamines
Hypoglycemic agents	Cocaine	Caffeine	Carbamates	Ethanol	Cocaine
Opioids	Cyclic antidepressants	Carbon monoxide	Clonidine	Isopropyl alcohol	Cyclic antidepressants
Phenothiazines	Drug withdrawal	Clonidine	Cyclic antidepressants	Organophosphates	Dopamine
Colchicine	LSD	Cocaine	Digoxin	Opioids (meperidine	Drug withdrawal
Akee fruit poisoning	Monamine oxidase inhibitors	Cyanide	Lithium	may cause mydriasis)	Glutethimide
Lithium	Phencyclidine (PCP)	Cyclic antidepressants	Metoclopramide	PCP	LSD
	Psychotropics (Neuroleptic	Drug withdrawal	Opioids	Phenothiazines	Monamine oxidase inhibitors
	malignant syndrome)	Ephedrine	Organophosphates	Physostigmine	PCP
	Phenothiazines	Hydrogen sulfide	Phenylpropanolamine	Pilocarpine	
	Butyrophenones	Phencyclidine (PCP)	Physostigmine		
	Clozapine/Olanzapine	Phenothiazines	Propoxyphene		
	Risperidone	Pseudoephedrine	Quinidine		
	Salicylates	Theophylline			
	Serotoninerigc antidepressants	Thyroid hormone			
	Serotonin syndrome				

Table 3
Selected drugs that alter mental status and muscle tone

Depressed physiologic state	Agitated physiologic state	Delirium and confusion	Dystonic reactions	Dyskinesias	Rigidity
Sympatholytics	Sympathomimetics	Alcohol/drug	Haloperidol	Anticholinergics	Black widow
Adrenergic blockers	Adrenergic agonists	withdrawal	Metoclopramide	Cocaine	spider bite
Antiarrhythmics	Amphetamines	Anticholinergics	Olanzapine	PCP	Neuroleptic
Antihypertensives	Caffeine	Antihistamines	Phenothiazines	Risperidone	malignant syndrome
Antipsychotics	Cocaine	Carbon monoxide	Risperidone		PCP
Cyclic antidepressants	Ergot alkaloids	Cimetidine			Fentanyl
Cholinergics	Monoamine oxidase	Heavy metals			
Bethanecol	inhibitors	Lithium			
Carbamates	Theophylline	Salicylates			
Nicotine	Anticholinergics				
Organophosphates	Antihistamines				
Physostigmine	Antiparkinsonian drugs				
Pilocarpine	Antipsychotics				
Sedative-hypnotics	Antispasmotics				
Alcohols	Cyclic antidepressants				
Barbiturates	Cyclobenzaprine				
Benzodiazepines	Drug withdrawal				
γ-hydroxybutyrate	β-blockers				
Ethchlorvynol	Clonidine				
Narcotics	Ethanol				
Analgesics	Opioids				
Antidiarrheal agents	Sedative-hypnotics				
Other	Hallucinogens				
Carbon monoxide	LSD				
Cyanide	Marijuana				
Hydrogen sulfide	Mescaline				
Hypoglycemic agents	Phencyclidine				
Lithium	Other				
Salicylates	Thyroid hormones				

Box 2. Common causes of abnormal anion gap

Increased anion gap

- Lactic acidosis (type A)
- Uremia
- Sepsis
- Rhabdomyolysis
- Ketoacidosis
  - Diabetic
  - Alcoholic
  - Starvation
- Toxic ingestions
  - Ethylene glycol
  - Methanol
  - Paraldehyde
  - Salicylate
- Metabolic alkalosis with volume depletion

Decreased anion gap

- Increased unmeasured cation
  - Hyperkalemia
  - Hypercalcemia
  - Hypermagnesemia
  - Elevated IgG (myeloma, cationic paraprotein)
  - Acute lithium intoxication
- Decreased unmeasured anion
  - Hypoalbuminemia
- Drugs
  - Bromide
  - Iodide
  - Lithium
  - Polymyxin B
  - Tromethamine
- Analytical artifact
  - Hypernatremia (> 170 mEq/L)
  - Hyperlipidemia

the potential of exacerbating myoglobinuric renal tubular injury and is virtually never recommended.

Multi-dose activated charcoal

The American Academy of Clinical Toxicologists reported that although multi-dose charcoal significantly enhances drug elimination, it has not yet been evaluated in controlled trials of poisoned patients. It can be considered in patients who have a life-threatening ingestion of carbamazepine, dapsone, phenobarbital, quinine, or theophylline [24].

Extracorporeal removal of toxins

Extracorporeal removal is considered when a toxin is projected to undergo delayed or insufficient clearance because of organ dysfunction, the intoxicant produces toxic metabolites, or delayed toxicity is characteristic of the intoxication. Depending on the situation, hemodialysis, hemoperfusion, or hemofiltration are recommended. A complete list of drugs and toxins that are amenable to extracorporeal removal is beyond the scope of this article [4].

Box 3. Selected drugs that are associated with an increased anion gap or metabolic acidosis

- Acetaminophen (>75 g)
- Amiloride
- Ascorbic acid
- Carbon monoxide
- Chloramphenicol
- Colchicine
- Cyanide
- Dapsone
- Epinephrine
- Ethanol
- Ethylene glycol
- Formaldehyde
- Hydrogen sulfide
- Iron
- Isoniazid
- Ketamine
- Metformin
- Methanol
- Niacin
- Nitroprusside
- NSAIDs
- Papaverine
- Paraldehyde
- Phenformin
- Propofol
- Salicylates
- Terbutaline
- Tetracycline (outdated)
- Toluene (hippuric acid)

Box 4. Drugs and toxins that associated with an increased osmolal gap

- Ethanol (if not included in the calculation of serum osmolality)
- Ethylene glycol/glycolaldehyde
- Glycerol
- Glycine
- Isopropanol/acetone
- Mannitol
- Methanol/formaldehyde
- Propylene glycol
- Radiocontrast media
- Hypermagnesemia (>9.5 mEq/L)
- Sorbitol

Antidotes

Table 4 lists antidotes for specific drugs and poisons.

Indications for intensive care unit admission

Routine admission of the poisoned patient to the intensive care unit (ICU) is not necessary [25–27]. Box 5 provides a list of criteria for ICU admission [4].

Specific poisonings

Acetaminophen

Acetaminophen (paracetamol) is the most common medicinal overdose reported to poison information centers. Most exposures are not associated with significant morbidity or mortality; however, acetaminophen can cause severe and fatal hepatic injury.

Acetaminophen toxicity is due to a metabolite, n-acetyl-p-benzoquinonimine (NAPQI), that is rapidly detoxified by conjugating irreversibly with the sulfhydryl group of glutathione and excreted in the urine as mercapturic acid and cysteine conjugates. In overdose, glutathione is depleted and NAPQI is not detoxified. The toxic metabolite binds to macromolecules of hepatocytes which induces centrilobular hepatic necrosis with periportal sparing. Single doses of 150 mg/kg (7.5 to 10 g) in adults and 200 mg/kg in children are considered toxic [28,29]; 4 to 6 g can be toxic in alcoholics, patients who have underlying liver disease, and patients who are malnourished with depleted glutathione levels.

There are four phases of acetaminophen toxicity [28]. Phase I (first 24 hours) is characterized by anorexia, malaise, diaphoresis, nausea, and vomiting. Phase II occurs 24 to 48 hours after untreated overdose with right upper quadrant pain and abnormal liver

Table 4
Antidotes for selected drug and poisons

Drug/poison	Antidotes
Acetaminophen	N-acetylcysteine
Anticholinergics	Physostigmine
Anticholinesterases	Atropine
Benzodiazepines	Flumazenil
Black widow spider bite	Equine-derived antivenin
Carbon monoxide	Oxygen
Coral snake (Eastern and Texas) bite	Equine-derived antivenin
Cyanide	Amyl nitrite, sodium nitrite, sodium thiosulfate, hydroxycobalamin
Digoxin	Digoxin-specific antibodies[a]
Ethylene glycol	Ethanol/fomepizole, thiamine, and pyridoxine
Heavy metals (arsenic, copper, gold, lead, mercury)	Dimercaprol, EDTA, penicillamine
Hypoglycemic agents	Dextrose, glucagon, octreotide
Iron	Deferoxamine mesylate
Isoniazid	Pyridoxine
Methanol	Ethanol or fomepizole, folic acid
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Organophosphate	Atropine, pralidoxamine
Rattlesnake bite	Equine-derived antivenin

[a] Digoxin-specific antibodies are indicated for severe ventricular arrhythmias, bradyarrhythmias that are unresponsive to atropine, ingestion of more than 10 mg of digoxin in adults, steady-state concentration >10 ng/ml, and progressive potassium elevation that is greater than 5 mEq/L.

Box 5. Criteria for admission of the poisoned patient to the ICU

- Respiratory depression (eg, $PaCO_2 > 45$ mm Hg)
- Emergency intubation
- Seizures
- Cardiac arrhythmia (second or third degree atrioventricular block)
- Systolic blood pressure that is less than 80 mm Hg
- Unresponsiveness to verbal stimuli
- Glasgow Coma Scale score that is less than 12
- Need for emergency dialysis, hemoperfusion, or extracorporeal membrane oxygenation
- Increasing metabolic acidosis
- Pulmonary edema induced by toxins (including inhalation) or drugs
- Hypothermia or hyperthermia, including neuroleptic malignant syndrome
- Tricyclic or phenothiazine overdose that manifests anticholinergic signs, neurologic abnormalities, QRS duration of greater than 0.12 seconds, or QT that is greater than 0.5 seconds
- Body packers and stuffers
- Concretions and bezoars caused by drugs (verapamil, nifedipine, theophylline, clomipramine, enteric coated aspirin)
- Emergency surgical intervention
- Administration of pralidoxime in organophosphate toxicity
- Antivenin administration in *Crotalidae*, coral snake, or arthropod envenomation
- Need for continuous infusion of naloxone
- Hypokalemia secondary to digitalis overdose (or need for digoxin-immune antibody Fab fragments)

function tests. Phase III (48 to 96 hours) is characterized by severe hepatotoxicity: encephalopathy, coagulopathy, hypoglycemia, and peak liver function abnormalities. Phase IV involves recovery, liver transplantation, or death.

The modified Rumack-Matthew nomogram helps predict acetaminophen hepatotoxicity (Fig. 1) [30]. This nomogram stratifies patients into three categories: probable hepatic toxicity, possible hepatic toxicity, and no hepatic toxicity. It is valid only in single acute ingestions and is based on the relationship between acetaminophen level and time after ingestion. When this relationship is known, n-acetylcysteine is indicated for acetaminophen levels above the lower line. The lower line defines plasma levels that are 25% below those that are expected to cause hepatotoxicity. Points between the lower line and a parallel middle line suggest possible risk for hepatotoxicity; points above the middle line, but below a parallel upper line represent probable risk; points above the upper line suggest high risk. N-acetylcysteine is also indicated if the acetaminophen level is greater than 5 μg/mL with an unknown time of ingestion (but less than 24 hours), if acetaminophen levels are not available, or there is evidence of hepatotoxicity. The nomogram is of limited use when: (1) an acetaminophen level is obtained within 4 hours of ingestion because of ongoing drug absorption and distribution; conversely patients who present late may have undetectable levels despite a

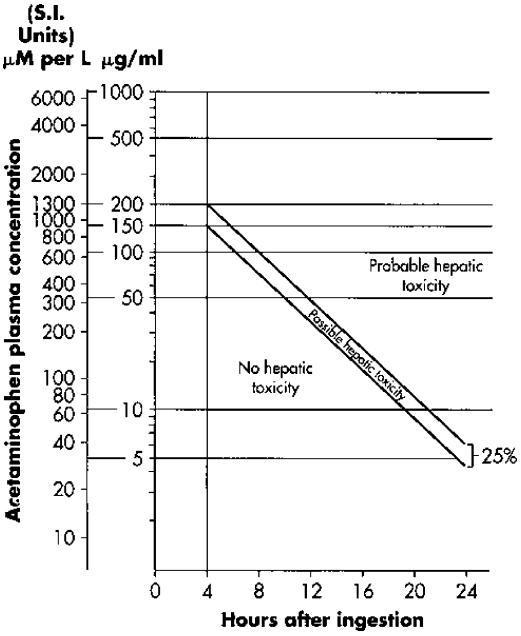

Fig. 1. The Rumack-Matthew nomogram for predicting acetaminophen hepatotoxicity. (*From* Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975;5: 873; with permission)

lethal dose; (2) there is chronic ingestion or overdose with an extended-release preparation [31–33]; (3) a patient has induced cytochrome P-450 enzymes, is malnourished, or has depleted glutathione stores (as in recent sublethal acetaminophen ingestion) [34,35]; and (4) the time of ingestion is not known. Bond and Lite [36] reported that the Rumack-Matthew nomogram could not be used in almost half of patients who were hospitalized for acetaminophen ingestion and an even higher proportion of those who had bad outcomes [36].

Gastric lavage is reasonable if performed within 60 minutes of acetaminophen ingestion; however, activated charcoal that is administered once is the modality of choice for gastric decontamination. Activated charcoal likely does not decrease the efficacy of N-acetylcysteine [37,38], and may reduce the need for N-acetylcysteine administration in rare cases [39]. N-acetylcysteine is virtually 100% effective when administered within the first 8 to 10 hours [40], although benefits may be seen for up to 24 hours after ingestion and even after the onset of hepatic failure [41,42]. An initial oral loading dose of 140 mg/kg of N-acetylcysteine (mixed with juice) is followed by maintenance dose of 70 mg/kg every 4 hours for 17 doses. If vomiting occurs, the dose should be repeated with an antiemetic, such as metoclopramide or ondansetron. Occasionally, a nasogastric tube may be necessary or the drug can be considered for intravenous (IV) administration; both routes of administration are efficacious [43]. The IV formulation is routinely used in Europe but has not been approved by the United States Food and Drug Administration (FDA) [44]. Yip et al [45] reported the IV use of the oral N-acetylcysteine in 76 patients using a micropore filter. Four patients had adverse reactions; none were life-threatening. Minor reactions of flushing, urticaria, angioedema, and respiratory symptoms were treated with IV diphenhydramine and β_2-agonist bronchodilators. Anaphylactoid reactions with IV drug have been reported [46]. Limited data support the safety and efficacy of short course treatment in certain cases [47]. Protocols using a 20 hour–IV course and a 48 hour–IV course were safe and effective [48,49].

Acetaminophen-induced fulminant hepatic failure is one the most common reasons for liver transplantation [50]. Nevertheless, for patients who have acute fulminant hepatic failure who do not undergo liver transplantation, those with acetaminophen-induced fulminant hepatic failure have the highest survival rate (57%). [51] An acute Physiology and Chronic Health Evaluation (APACHE)-II score of 15 or greater identifies patients who are at risk for mortality and the need for timely consideration for liver transplantation [52,53].

Nonethanol alcohols

Nonethanol alcohol ingestion typically results in inebriation. For ethylene glycol and methanol, cardinal features include a metabolic acidosis with an increased anion gap or presence of an increased osmolal gap. Serious intoxication rarely occurs without increasing the anion gap when there is insufficient time for acid metabolites to form, or when a patient starts with a low baseline gap.

Ingestion of as little as 100 mL of ethylene glycol can be lethal in an adult patient; serum levels that are greater than 50 mg/dL are associated with significant toxicity. Ethylene glycol is metabolized by alcohol dehydrogenase to glycoaldehyde and glycolic acid, and ultimately, to glyoxylic acid and oxalic acid. Poisoning with this alcohol results in a triphasic clinical course: stage 1 (30 minutes to 12 hours postingestion) consists of inebriation, ataxia, seizures, variable levels of anion gap increase with metabolic acidosis, Kussmaul's breathing, an elevated osmolal gap, crystalluria, and hypocalcemia. Cerebral edema causes coma or death. Stage 2 (12 to 24 hours) is dominated by myocardial dysfunction with high- or low-pressure pulmonary edema. Stage 3 (2 to 3 days) is dominated by acute renal failure that is due to acute tubular necrosis with an element of tubular obstruction from calcium oxalate precipitation [54–56]. Late (6 to 18 days) neurologic sequelae have been described in survivors [57,58].

The primary toxin that results from methanol metabolism is formic acid. As little as 30 mL of methanol can cause significant toxicity; lethal serum levels of 80 to 100 mg/dL can be reached by ingesting approximately 150 to 240 mL of a 40% solution. Methanol causes an initial period of headache, inebriation, dizziness, ataxia, and confusion. Further accumulation of formic acid (6 to 72 hours) leads to increases in the anion gap and visual symptoms become more pronounced. Visual loss or optic nerve swelling suggests methanol intoxication. Pancreatitis is an additional feature of methanol poisoning [59,60]. Symptoms of ethylene glycol and methanol poisoning may be delayed if there is concurrent ethanol consumption; this inhibits conversion of these compounds to their toxic metabolites.

Halting the further metabolism of ethylene glycol and methanol to toxic metabolites can be achieved by inhibiting the enzyme alcohol dehydrogenase [61]. Fomepizole and ethanol are effective inhibitors of alcohol dehydrogenase. Fomepizole does not exacer-

bate the inebriated state and does not require blood level monitoring [62–64]. It is administered as a 15 mg/kg IV loading dose followed by a 10 mg/kg IV bolus every 12 hours. After 48 hours, the bolus dose should be increased to 15 mg/kg every 12 hours to account for enhanced fomepizole metabolism. For ethylene glycol and methanol, patients are treated until serum levels decrease to less than 20 mg/dL.

Hemodialysis can be performed concurrently with fomepizole if clinically indicated. In ethylene glycol poisoning, hemodialysis is indicated when ethylene glycol levels exceed 50 mg/dL, when there is significant and refractory metabolic acidosis, or when there is end organ damage. Dialysis is continued until ethylene glycol levels are undetectable and acidosis has resolved. In methanol poisoning, hemodialysis is indicated when methanol levels exceed 50 mg/dL, a lethal dose has been ingested, there is significant and refractory metabolic acidosis, or when there is end organ damage. Dialysis is continued until acidosis has resolved and methanol levels decrease to less than 25 mg/dL. Other supportive measures include gastric lavage in the first hour post-ingestion, correction of hypocalcemia and hypoglycemia, and thiamine, folate, and pyridoxine supplementation. Bicarbonate has not been shown to improve outcome.

Isopropanol is highly suspected when there is a combination of ketonemia, ketonuria, absence of an increased anion gap or metabolic acidosis, hemorrhagic gastritis, and an increased osmolal gap [65]. A serum isopropanol level confirms the diagnosis. Supportive measures usually suffice in the treatment of these patients. Gastric lavage may be helpful if performed early. Hemodialysis is necessary when lethal doses have been ingested (150–240 mL of 40%–70% solution), lethal levels are detected (400 mg/dL), or there is refractory shock [66]. Fomepizole is not indicated in isopropanol poisoning.

Amphetamines

During the past decade methamphetamine use has increased rapidly in the United States, particularly in inner city areas [67]. Common amphetamine and amphetamine-like prescription drugs include methylphenidate, dextroamphetamine, and pemoline, that are used primarily for narcolepsy and attention-deficit disorder and various anorectic medications that are used for weight loss (eg, diethylpropion, phentermine). Illicit drugs include methamphetamine (‘‘crank’’ or ‘‘ice’’) and 3,4-methylenedioxymethamphetamine (MDMA; ‘‘ecstasy’’). Emergency department visits that are due to MDMA (ecstasy) abuse increased from 253 visits in 1994 to 5542 reports in 2001. Methamphetamine abuse has remained stable [68].

Amphetamines are central nervous system (CNS) stimulants that release catecholamines, inhibit the reuptake of catecholamines, or inhibit monoamine oxidase. Intoxication can manifest as confusion, tremor, anxiety, agitation, irritability, mydriasis, tachyarrhythmias, myocardial ischemia, hypertension, hyperreflexia, hyperthermia, rhabdomyolysis, renal failure, coagulopathy, seizures, and hepatotoxicity [69–72]. Hyperthermia, arrhythmias, status epilepticus, intracranial hemorrhage, fulminant liver failure, and aspiration pneumonitis can all lead to death [73].

Treatment is supportive and includes: (1) maintenance of airway; (2) managing hypertension with systemic vasodilators, such as phentolamine or nitroprusside; (3) controlling tachyarrhythmias with a β-blocker; (4) controlling agitation and violent behavior with butyrophenones, such as haloperidol or droperidol, benzodiazepines, or phenothiazines; and (5) control of hyperthermia with active cooling measures, if necessary. Droperidol may achieve more rapid and profound sedation than lorazepam in this setting [74]. The value of dantrolene is debated [75–77]. Activated charcoal should be administered promptly with a cathartic. Gastric lavage is useful if performed within 1 hour of ingestion. Dialysis and hemoperfusion are not effective.

Carbon monoxide

Although there has been a slight decline in deaths as a result of carbon monoxide (CO) poisoning, it remains the most common cause of death by poisoning in the United States. Twenty percent of deaths that are due to this poisoning are considered to be accidental and unintentional in nature [78].

Mild carboxyhemoglobinemia (5%–10%) results in headache and mild dyspnea. Levels between 10% and 30% cause headache, dizziness, weakness, dyspnea, irritability, nausea, and vomiting. Coma, seizures, cardiovascular collapse, and death occur with carboxyhemoglobin concentrations that are greater than 50%. Carboxyhemoglobin levels do not always correlate with clinical severity. Delayed neuropsychiatric sequelae (DNS) develop in 10% to 30% of survivors [79–81]. DNS can occur from 3 to 240 days after apparent recovery. Manifestations include persistent vegetative state, parkinsonism, short-term memory loss, behavioral changes, hearing loss, incontinence, and psychosis. There is no accurate way of predicting which patients will develop DNS; some patients recover [81].

Carboxyhemoglobin levels should be determined by co-oximetry [82]. Pulse oximetry cannot accurately distinguish carboxyhemoglobin from oxyhemoglobin which leads to an overestimation of oxyhemoglobin and a potentially delayed diagnosis [83,84].

Providing 100% supplemental oxygen decreases the half-life of carboxyhemoglobin from 5 to 6 hours on room air to 40 to 90 minutes. Hyperbaric oxygen (2.8 atmospheres within 6 hours of exposure) further decreases the half-life of carboxyhemoglobin to 15 to 30 minutes. The role of hyperbaric oxygen in the management of CO poisoning has been debated and recently reviewed [85]. Evidence from randomized, controlled trials is insufficient to provide clear guidelines [86]. Recently, a large, double-blind, randomized, controlled trial of hyperbaric oxygen treatment versus normobaric oxygen treatment in CO poisoning demonstrated that three hyperbaric oxygen treatment sessions (2 to 3 atmospheres at intervals of 6 to 12 hours) within 24 hours of exposure reduced DNS at 6 weeks and 12 months [87]. Patients who have potentially life-threatening exposures should be considered for hyperbaric treatment if a chamber is readily available [88].

Cocaine

Cocaine inhibits neuronal uptake of catecholamines which leads to CNS stimulation. Common manifestations of toxicity include euphoria, anxiety, agitation, psychosis, delirium, seizures, chest pain, arrhythmias, myocardial infarction, and cerebrovascular accidents [89]. Other cardiovascular manifestations of cocaine include sudden death, congestive heart failure, pulmonary hypertension, endocarditis, and aortic dissection [90]. Currently, there are no clinical parameters that can reliably identify patients who are at low risk for myocardial infarction; this mandates that all patients who have cocaine-associated chest pain be evaluated for myocardial infarction and undergo a minimal observation and monitoring of 9 to 12 hours before discharge [91,92]. Respiratory complications of cocaine include status asthmaticus, upper airway obstruction, pulmonary hypertension, barotrauma, pulmonary edema, and alveolar hemorrhage. Inhalation of crack cocaine can cause an acute pulmonary syndrome that is characterized by dyspnea, diffuse infiltrates, acute asthma and hemoptysis [93]. Rhabdomyolysis with myoglobinuria also occurs [94].

The most important strategy in cocaine intoxication is rapid treatment of hyperthermia, seizures, and agitation. Active and passive patient cooling, sedation, and muscle paralysis may be necessary. For orally-ingested drug, activated charcoal should be given to decrease further drug absorption. Cocaine-associated chest pain may be treated with nitrates and calcium-channel blockers [95]. β-blockers administered alone (including labetolol) should be avoided because of the blockade of β_2-mediated vasodilatation and unopposed α-adrenergic stimulation (see references [90, 96–98]). The combination of nitroprusside and a β-adrenergic blocking agent, or phentolamine alone or in addition to a β-blocker may successfully treat myocardial ischemia and hypertension [99]. Respiratory complications are treated in a supportive manner with bronchodilators for bronchospasm and chest tube placement for pneumothoraces [100].

Cyanide

Poisoning may occur through inhalation of hydrogen cyanide gas, a combustion by-product of cyanide-containing products, sodium nitroprusside infusion, and, rarely, absorption of cyanide-containing solutions or gas through the skin. The mechanism of toxicity involves the binding of cyanide to cellular cytochrome oxidase and resultant interference with aerobic oxygen use.

Cyanide is detoxified by enzymatic conversion to thiocyanate, a less toxic and renally-excreted metabolite. Small amounts of cyanide are also detoxified by hydroxycobalamin, which forms non-toxic cyanocobalamin.

Toxicity is manifested early on by anxiety, dyspnea, headache, confusion, tachycardia, and hypertension. Stupor or coma, seizures, fixed and dilated pupils, hypoventilation, hypotension, bradycardia, heart block, ventricular arrhythmias, and cardiopulmonary collapse soon follow.

Rapid diagnosis is dependant upon a high index of suspicion, often in the setting of smoke inhalation where combined CO and cyanide toxicity occurs. Blood cyanide levels that are greater than 0.5 mg/L are considered toxic [101]. The rapid onset of coma, seizures, and cardiopulmonary dysfunction with lactic acidosis or an elevated mixed venous oxyhemoglobin saturation (evidence of the blocking of aerobic oxygen use) suggests cyanide poisoning [102].

Early treatment can be life saving. Oxygen, decontamination, nitrites, and sodium thiosulfate are the main therapeutic modalities. One hundred percent F_IO_2, either by face-mask or endotracheal tube, should be instituted immediately. Hyperbaric oxygen is unproved in cyanide poisoning [103]. Amyl and sodium nitrites induce formation of methemoglobin. Cyanide has a high affinity for the ferric iron that is contained in methemoglobin, which thereby renders methemoglobin an effective scavenger of unbound cyanide. Typ-

ically methemoglobin levels remain less than 20% without significant reduction of total oxygen-carrying capacity [104]. Methylene blue should not be used to treat methemoglobinemia because it will release free cyanide. Sodium thiosulfate enhances conversion of cyanide to thiocyanate. [105] Although not approved by the FDA, hydroxycobalamin that is administered as a one-time IV dose of 4 to 5 grams seems to be capable of reducing red blood cell and plasma cyanide concentrations [106–109]. Gastric emptying is recommended for acute ingestions, followed by activated charcoal. Induced emesis is not recommended because of the risk of rapid, cyanide-induced deterioration in clinical status and subsequent risk of aspiration. Hemodialysis or hemoperfusion can only clear high levels of thiocyanate.

Cyclic antidepressants

Cyclic antidepressants are among the most commonly encountered causes of self-poisoning. In overdose, these drugs affect the central nervous and cardiovascular systems with potential to cause abrupt and unpredictable deterioration. Toxicity stems mainly from anticholinergic effects, inhibition of neural uptake of norepinephrine or serotonin, peripheral α-adrenergic blockade, and membrane depressant effects.

Cyclic antidepressant overdose should be considered in all patients who have QRS prolongation. Confirmation of exposure is available by urine toxicology screening. Blood levels are not generally followed because of the reliability of the QRS duration to predict severity. A limb-lead QRS interval that is longer than 0.10 seconds predicts seizures; a QRS duration that is longer than 0.16 seconds is associated with ventricular arrhythmias [110–112]. A maximal limb-lead QRS duration of less than 0.1 seconds is rarely associated with serious toxicity.

Treatment involves initial supportive measures followed by serum alkalinization with sodium bicarbonate (1–2 mEq/kg, IV) when there is widening of the QRS interval to decrease the fraction of free drug. Sodium bicarbonate should be continued until there is narrowing of the QRS interval or the serum pH exceeds 7.55. Hyperventilation is an alternate strategy in intubated patients. The ECG should be followed for 48 to 72 hours [113]. After initial stabilization, gastric lavage followed by activated charcoal is the preferred method of gastric decontamination. Emesis should not be induced because of the high risk of aspiration. Activated charcoal can be given without gastric lavage [114]; there is no role for multi-dose activated charcoal [115]. Hemodialysis and hemoperfusion are not effective.

Refractory ventricular arrhythmias should be treated with lidocaine, not phenytoin [116,117]. Vasopressor support may be necessary for refractory hypotension [118–120]. Pulmonary edema, both cardiogenic and noncardiogenic, has been reported and is treated supportively with positive pressure mechanical ventilation [121,122]. Pulmonary artery catheters can lead to arrhythmias and should be avoided. Metabolic acidosis from seizures or arrhythmias promotes unbinding of the drug from proteins and contributes to increased toxicity [123]. Therefore, seizures should be treated promptly with benzodiazepines and phenobarbital. Phenytoin should be reserved for refractory cases. Paralysis or deep sedation with propofol may be indicated for refractory seizures [124].

Death from cyclic antidepressant overdose occurs primarily from cardiac toxicity and tends to occur in the first 24 hours of arrival. Most patients develop symptoms within the first 6 hours [125]. Patients should remain in the ICU for 12 hours after discontinuation of treatment. They should be asymptomatic and demonstrate a normal ECG and arterial pH before transfer [126,127].

Gamma-hydroxybutyrate

γ-hydroxybutyrate (GHB), also known as "liquid ecstasy," "liquid G," "date-rape drug," or "fantasy," has become a popular drug of abuse among young individuals. GHB is derived from γ-aminobutyric acid (GABA) and is believed to function as an inhibitory transmitter through specific brain receptors for GHB, and, possibly, through GABA receptors [128],

Clinical manifestations of GHB depend on the dose ingested. Low doses of GHB can induce a state of euphoria. Emesis, hypothermia, bradycardia, hypotension, and respiratory acidosis have all been described [129]. Higher doses can result in deep coma and death. [130]

Treatment of GHB poisoning is mainly supportive. Patients may have coingested other drugs of abuse, especially ethanol and amphetamines [129]. Mechanical ventilation may be necessary for a short period of time; most patients regain consciousness spontaneously within 5 hours of ingestion [129]. Naloxone and flumazenil are not helpful. Yates and Viera [131] described the use of physostigmine, 2 mg IV, in the emergency department to reverse coma in two patients who had GHB overdose. Both patients awoke in less than 5 minutes after the administration of a single dose of physostigmine. The use of physostigmine is controversial because rapid recovery is the norm and there are risks, particularly when there is coingestion of a cyclic antidepressant [132].

Laboratory diagnosis of GHB ingestion is a challenge. Specialized laboratories can detect GHB in urine and blood by gas chromatography-mass spectroscopy [133,134] or by hair analysis [135].

Methemoglobinemia

Methemoglobin is formed by oxidation of circulating hemoglobin. Contrary to reduced (Fe^{2+}) hemoglobin, methemoglobin (Fe^{3+}) is incapable of binding and transporting oxygen. Acquired life-threatening methemoglobinemia generally occurs in the setting of oxidant drugs (eg, topical anesthetics) or toxin exposure (Box 6).

Box 6. Selected drugs and toxins that are associated with acquired methemoglobinemia

Amyl nitrite
Butyl nitrite
Bromates
Aniline dyes
Benzocaine
Bupivacaine
Chlorates
Chloroquine
Dapsone
Flutamide
Herbicides
Isobutyl nitrite
Isosorbide dinitrate
Lidocaine
Methyl nitrite
Metoclopramide
Nitric oxide
Nitroethane
Nitrobenzene
Nitroglycerin
Nitroprusside
Pesticides
Phenacetin
Phenazopyridine
Prilocaine
Primaquine
Silver nitrate
Sodium chlorite
Sodium nitrite
Sulfonamides

In mild methemoglobinemia (< 15% of the total hemoglobin), patients generally remain asymptomatic despite evidence of cyanosis. Higher methemoglobin concentrations result in dyspnea, headache, and weakness. Severe methemoglobinemia (>60%) is associated with confusion, seizures, and death. Arterial blood gases with co-oximetry measure methemoglobin levels. With high methemoglobin levels (eg, 35%), oxygen saturation by pulse oximetry trends toward 85% and plateaus at that level despite further increments in methemoglobin [10]. Conversely, mild methemoglobinemia may result in a falsely low oxygen reading by pulse oximetry. In addition, methylene blue can also cause a false elevation in methemoglobin level as measured by co-oximetry and pulse oximetry [136]. "Chocolate-colored" venous blood that does not change color on exposure to air is another clue to methemoglobinemia [137].

The preferred mode of gastric decontamination is gastric lavage followed by activated charcoal. Methylene blue, a dye that is capable of reversing drug/toxin-induced methemoglobinemia by increasing conversion of methemoglobin to hemoglobin, should be considered in symptomatic patients. Excessive doses of methylene blue may paradoxically increase oxidant stress and methemoglobinemia. Contraindications to methylene blue include glucose-6-phosphate dehydrogenase deficiency, renal failure (because of the renal excretion of the antidote), and reversal of nitrite-induced methemoglobinemia during treatment of cyanide poisoning. Failure to respond to methylene blue suggests cytochrome b5 reductase deficiency, glucose-6-phosphate dehydrogenase deficiency, or sulfhemoglobinemia. Administration of methylene blue in patients who have glucose-6-phosphate dehydrogenase deficiency can lead to hemolytic anemia. In severe cases where methylene blue is ineffective (because of the above-mentioned conditions), clinicians need to consider additional therapies of possible value, such as exchange transfusion and hyperbaric oxygen [138].

Opioids

Stimulation of opiate receptors causes generalized depression of the CNS. Symptoms range from lethargy to respiratory arrest and coma. Respiratory failure can arise through a variety of mechanisms including alveolar hypoventilation, aspiration pneumonitis, and noncardiogenic pulmonary edema [139,140]. Noncardiogenic pulmonary edema occurs early in the course of acute overdose and may also be caused by treatment with naloxone. Approximately one third of patients who have heroin-induced noncardiogenic pulmonary

edema require short-term mechanical ventilation [141]. Inhaled heroin also triggers status asthmaticus [142–144]. Opioids additionally cause hypotension, bradycardia, decreased gut motility, rhabdomyolysis, muscle flaccidity, hypothermia, and seizures. Normeperidine, a metabolite of meperidine, lowers the seizure threshold [145,146].

Most opioid-related deaths occur in young individuals who chronically abuse heroin [147,148]. A minority of deaths (17%) occurs in first-time users [149]. Co-ingestion of other drugs is common [150].

The diagnosis of opioid overdose is often made on clinical grounds [151]. Small, ''pin-point'' pupils that respond to naloxone are highly suggestive. Opioid exposure can be easily confirmed by urine toxicology screening; however, certain opioids, such as fentanyl, are not detected by routine urine toxicology screening.

Lack of miosis does not rule out opioid poisoning; co-existing toxins or concurrent problems, like anoxic brain injury, may confound the picture. It is also true that not every patient who responds to naloxone has an opiate overdose and not every patient with an opiate overdose responds to naloxone. Naloxone is obviously helpful in opioid overdose, but its indiscriminate use should be discouraged [152].

After initial supportive measures, gastric lavage should be performed in cases of oral ingestion. The usefulness of gastric lavage may extend to several hours postingestion because of decreased gut motility [21]. Activated charcoal follows gastric lavage. Naloxone is administered at an initialdose of 0.2 to 0.4 mg IV. Endotracheal use has also been described [153]. A lower initial dose avoids acute withdrawal in chronic abusers. If naloxone does not produce a clinical response after 2 to 3 minutes, an additional 1 to 2 mg IV may be administered to a total dose of 10 mg. In general, a lack of response to 10 mg naloxone is required to exclude opioid toxicity, although doses that are greater than 10 mg may be required to antagonize the effects of propoxyphene, diphenoxylate, methadone, and pentazocine [154]. Opioid antagonism typically occurs within minutes of naloxone administration and lasts for 45 to 90 minutes. Therefore, repeat boluses or a continuous naloxone infusion may be required (0.4–0.8 mg/hour). Supplemental oxygen and mechanical ventilation may be required in cases of pulmonary edema [139]. Diuresis may aggravate hypotension.

Organophosphates and carbamate insecticides

Most insecticides that are used in the United States are organophosphates (also used as warfare nerve agents) or carbamates. These compounds are rapidly degraded in the environment. Both compounds exert their toxicity through inhibition of acetylcholinesterase (AChE) and accumulation of acetylcholine at synapses. Organophosphates are irreversible inhibitors of AChE; carbamates are reversible inhibitors.

Although most intoxications occur through the gastrointestinal tract, insecticides can also be absorbed rapidly through the skin [155], conjunctiva, and respiratory tract [156]. In the United States most exposures are accidental, but in some countries, organophosphates are used for suicide [157].

Toxicity is evident within the first 12 to 24 hours after exposure [158]. Cholinergic toxidrome that is induced by muscarinic overstimulation (SLUDGE: Salivation, Lacrimation, Urination, Diarrhea, GI cramps, Emesis) is the hallmark of organophosphate toxicity. Nicotinic overstimulation is more transient and presents with muscular weakness and fasciculations that can progress to paresis and paralysis, hypertension, and tachycardia. Signs include miosis, vomiting, salivation, respiratory distress, depressed mental status, and muscle fasciculations [159]. Tachycardia is more common than bradycardia [160]. Noncardiogenic pulmonary edema, arrhythmias, and conduction abnormalities also occur. An odor of garlic in the breath or sweat may be noted. Organophosphates, as opposed to carbamates, penetrate the blood–brain barrier and overstimulate central receptors which induces anxiety, confusion, seizures, psychosis, and ataxia.

Because of several limitations with measuring red blood cell AChE or pseudocholinesterase (PChE), the diagnosis of organophosphate poisoning remains a clinical one. These limitations include a falsely low PChE in patients who have liver disease, anemia, malnutrition, or a genetic variant (familial succinylcholine sensitivity). In addition, normal levels of enzyme activity do not exclude poisoning because of wide variations in normal levels [161]. Furthermore, plasma AChE level may not correlate with the severity of intoxication [162].

During initial stabilization, special attention should be paid to the respiratory status. Bronchoconstriction, excess secretions, muscle weakness, and altered mental status increase the risk of respiratory failure. In agricultural exposures it is extremely important to remove all contaminated clothing and cleanse the hair and skin thoroughly to decrease absorption. Health care workers must take precautions to protect themselves from accidental exposure by wearing protective gloves and gowns [155]. Gastric lavage may be useful if done immediately postingestion. Activated charcoal is indicated to limit further drug absorption

Symptomatic patients should receive atropine. Treatment should not await results of AChE or PChE levels. Atropine competitively blocks acetylcholine at muscarinic receptors, but has no effect on nicotinic receptors. Atropine crosses the blood–brain barrier and can cause CNS toxicity. Effects are difficult to distinguish from organophosphate poisoning. In this situation, the use of an anticholinergic that does not cross the blood–brain barrier (eg, glycopyrrolate) allows for further anticholinergic administration without CNS effects [163]. The dose of atropine that is required to achieve atropinization (mydriasis, dry mouth, increased heart rate) varies considerably, depending on the severity of poisoning. Dosages of up to 40 mg/day are not uncommon. If atropinization occurs after 1 to 2 mg of atropine, the diagnosis of acetylcholinesterase inhibitor poisoning should be questioned. The initial dose of atropine is 2 mg IV (6 mg IV for life-threatening cases) followed by 2 mg every 15 minutes until adequate atropinization has occurred.

Pralidoxime reverses the muscarinic and nicotinic effects of organophosphate poisoning. In carbamate poisoning, pralidoxime is generally not needed because of rapid resolution of symptoms and the reversible nature of enzyme inhibition. Pralidoxime reactivates phosphorylated cholinesterase enzyme and protects the enzyme from further inhibition. Administration before irreversible inactivation of cholinesterase is crucial, preferably within the first 6 hours of poisoning. Pralidoxime is still effective in the first 24 to 48 hours after exposure, especially when highly lipophilic organophosphates have accumulated in fat and are gradually released. After this critical period of time, restoration of cholinesterase function requires regeneration of the enzyme, a process that may take weeks to complete. The antimuscarinic effects of pralidoxime allow for faster atropinization with lower doses of atropine. The initial dose of pralidoxime is 1 to 2 g IV over approximately 10 to 20 minutes. Clinical response should be evident in less than 30 minutes. In cases where there is no improvement in muscle fasciculations or weakness, the same dose can be repeated in 1 hour. A continuous infusion is then administered at a rate of 200 to 500 mg/hour, and titrated to achieve the desired effect. Continuous infusion of pralidoxime may be necessary for more than 24 hours, depending on the half-life and lipid solubility of the poison, after which the dose may be gradually reduced and stopped while the patient is observed for signs of recurrent muscle weakness.

On average, most patients will require 5 to 14 days of intensive care monitoring. Recovery from carbamate poisoning is quicker than recovery from organophosphate poisoning. Between 60% and 70% of patients will require mechanical ventilation. Mortality has been reported between 15% and 36% [164,165].

Salicylates

Salicylates are common ingredients in a variety of prescription and nonprescription preparations. Clinical features of aspirin intoxication occur in most people who have serum levels that are greater than 40 mg/dL; in chronic intoxication, severe poisoning occurs at lower serum levels (particularly in the elderly). At toxic levels, salicylates uncouple oxidative phosphorylation and interfere with the Krebs cycle [166].

Minor intoxication causes tinnitus, vertigo, nausea, vomiting, and diarrhea. Significant ingestions in adults result in respiratory alkalosis or a mixed metabolic acidosis and respiratory alkalosis [167,168]. Respiratory alkalosis occurs through direct central stimulation. Other effects include noncardiogenic pulmonary edema, mental status changes, seizures, coma, gastrointestinal bleeding, liver and renal failure, hypoglycemia, and death [169]. In critically ill patients, neurologic abnormalities occur in 61% of patients, acid-base disturbances occur in 50% of patients, pulmonary complications occur in 43% of patients, coagulation disorders occur in 38% of patients, fever occurs in 20% of patients, and circulatory disorders, such as hypotension, occur in 14% of patients [170]. ICU mortality has been reported to be 15% [170].

The lethal adult dose is approximately 10 to 30 g or 150 mg/kg (35 tablets or more). Lethality correlates poorly with serum levels. A critical review of the commonly used Done nomogram [171] revealed that is of no value in the assessment of acute or chronic salicylism [172]. Its use may be misleading when there is an incorrect time of ingestion, ingestion of more than a single dose, or use of enteric-coated preparations [173]. Elderly patients are at risk for unintentional poisoning; a high index of suspicion is thus required to avoid delays in diagnosis that may contribute to higher mortality [174]. Patients who have chronic intoxication may present with CNS injury [175], noncardiogenic pulmonary edema [176], or isolated increase in the prothrombin time.

Management of a salicylate poisoning depends on whether the exposure is acute or chronic. Gastric lavage and activated charcoal (1 g/kg) are useful for acute ingestions, but not in cases of chronic salicylism. IV bicarbonate to increase plasma pH to between 7.45 and 7.5 induces urinary alkalinization and increases renal clearance [177]. This decreases the half-life of salicylates from 20 to 24 hours to less than 8 hours. Serial salicylate levels should be obtained to confirm a

response. Indications for hemodialysis include a serum level that is greater than 120 mg/dL acutely, or greater than 100 mg/dL 6 hours postingestion, refractory acidosis, coma, seizures, pulmonary edema, volume overload, and renal failure [178]. In chronic overdose, hemodialysis may be necessary for a symptomatic patient who has a serum salicylate level that is greater than 60 mg/dL.

Toxicity from weapons of warfare and terrorism

Unfortunately, there is a variety of chemical, biological, microbiological, and nuclear toxins that can be used in a terrorist attack [179–183]. Although it is beyond the scope of this article to cover every toxin exposure in detail, we intend to familiarize the critical care physicians with the most likely ones.

Chemical agents

Nerve agents

Nerve agents are classically divided into G agents (first synthesized in Germany) and V agents (V for "venom"). Toxins in the G category include tabun (GA), sarin (GB), and soman (GD). The only toxin in the V category is VX [184]. Nerve agents are a class of organophosphates, and, therefore, affect synaptic transmission rather than neural structures per se; they can cause a cholinergic toxidrome. Nerve agents are liquid at normal temperatures; however, they can evaporate quickly (G agents faster than VX). They can be spread by artillery shells, rockets, and aerosol sprays and lead to contamination of food and water supplies [185]. Nerve agents are absorbed more rapidly through inhalation (seconds) than through skin contact or ingestion (hours) [186].

Treatment should consist of immediate supportive measures including the ABCs, limiting exposure to the toxins, atropinization, and administration of pralidoxime [187]. Skin decontamination is not necessary if exposure has been to vapor only (G agents). In general, because of the high volatility of G agents, exposed patients pose little risk to health care personnel. Liquid nerve agents must be neutralized from skin and hair to avoid continued absorption using a dilute bleach solution (one part household bleach containing 0.5% sodium hypochlorite plus nine parts water) [186]. In March of 1995 a terrorist attack in the Tokyo subway system exposed approximately 5000 Japanese citizens to sarin which overwhelmed several hospitals in the area [188]. Despite its high volatility, many Japanese health care workers developed symptoms of sarin exposure [189,190].

Blister/vesicant agents

The toxins in this category include: sulfur mustard (mustard gas), nitrogen mustard, and lewisite. Only the latter has a specific antidote, British antilewisite. Clinical presentations are similar; therefore, only sulfur mustard will be discussed.

Sulfur mustard or mustard gas

Sulfur mustard is a volatile yellow oily liquid that was used in mass quantities by Iraq during the Iran-Iraq conflict in the 1980s [191]. As an alkylating agent, it reacts readily and irreversibly with biologic proteins and nucleic acids. Unlike nerve agents that can kill instantly, these gases cause symptoms to occur hours, and even days, after exposure in a dose-dependent fashion. They tend to incapacitate more people than they kill. Major manifestations occur in the skin, the respiratory tract, and eyes. In the skin, large, thin-walled and easily ruptured blisters follow generalized erythema. Lesions are more severe in moist and warm areas, such as the groin and axillae. In the respiratory tract, inhalation injury can range from mild nasal mucosal irritation and tracheobronchitis to necrosis of the respiratory epithelium which leads to bronchopneumonia. Ocular symptoms include: lacrimation, conjunctivitis, photophobia, edema, and in severe cases, blindness [192,193].

Although not well studied, sodium thiosulfate has been used as a mustard scavenger and may prevent death if given within minutes of exposure [179,185]. Treatment is supportive and aimed at early decontamination with 0.5% sodium hypochlorite or large quantities of water. Large blisters are treated as a burn injury with silver sulfadiazine. Inhaled bronchodilators and systemic corticosteroids have been used for bronchospasm. Endotracheal intubation may be necessary for severe cases. Eyes should be irrigated thoroughly with water or normal saline. Bone marrow suppression may become evident in cases of significant exposure. Fortunately, fatality rates of only 2% to 4% have been reported [194].

Pulmonary agents

Agents in this category include: phosgene, sulfur dioxide, nitrogen dioxide, chlorine, and tear gas. When inhaled, these agents can cause acute lung injury and acute respiratory distress syndrome (ARDS), which may be delayed up to 24 hours. Treatment is supportive and includes mechanical ventilation. Experimental therapies in phosgene toxicity have included high does of ibuprofen, corticosteroids, aminophylline, and N-acetylcysteine (see references [179,185,195–197]).

Ricin

Ricin is a biological toxin (protein) that is derived from the production of castor oil [198]. It is a liquid that can contaminate water and food supplies or it can be aerosolized. When ingested in large quantities, ricin leads to hepatic, splenic, renal, and GI tract necrosis. Inhalation of ricin causes fever, chest tightness, cough, dyspnea, and respiratory failure that is due to ARDS in 4 to 8 hours after exposure. Treatment is supportive. In cases of ingestion, there may be a role for activated charcoal. There is no antidote or vaccine available. Mortality is dose-dependent and can occur at 36 to 72 hours postexposure [179,199]. Ricin poisoning can be diagnosed by specific serum ELISA [199].

Biological agents

Many organisms and their toxins have the potential to serve as weapons of mass destruction. The most common include anthrax and smallpox virus, which were recently reviewed extensively (see references [200–205]). Less attention has been paid to microbiological toxins, such as botulinum toxin [206], *Clostridium perfringens* toxin, plague [207], viral hemorrhagic fever viruses [208], tularemia [209], and agroterrorism (attacks on crops and livestock) [180–182]. A review of this topic is beyond the scope of this article.

Summary

Intoxications present in many forms including: known drug overdose or toxic exposure, illicit drug use, suicide attempt, accidental exposure, and chemical or biological terrorism. A high index of suspicion and familiarity with toxidromes can lead to early diagnosis and intervention in critically ill, poisoned patients. Despite a paucity of evidence-based information on the management of intoxicated patients, a rational and systematic approach can be life saving.

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